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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,370	11/21/2003	Donna T. Ward	PTS-0070US.P1	3593

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/719,370	WARD ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,22-25,33,38-44,119,120 and 122-124* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,22-25,33,38-44,118 and 122-124* is/are rejected.

7)☒ Claim(s) *119 and 120* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1-16-04*, 8/24/05, 11/1/04, 11/2/04, 2/14/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 5-16-06.

Claims 1, 3-8, 22-25, 33, 38-44, 119, 120 and 122-124 are pending in the instant application.

Election/Restrictions

Claims 47-54, 64-67, 70, 71, 77, 81-88, 91-118 and 121 have been withdrawn (and canceled) from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5-16-06.

Applicant's election without traverse of SEQ ID No. 446 in the reply filed on 5-16-06 is acknowledged.

Priority

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 10/304,126, fails to provide adequate support or enablement in the manner provided by the first paragraph

of 35 U.S.C. 112 for one or more claims of this application. No support can be found in the claimed priority document for SEQ ID NO. 446.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-25, 33, 37-44 and 122-124 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to compositions and methods comprising the administration of compounds that are 12-50 nucleobases in length and targeted to a nucleic acid molecule encoding HIF1α of SEQ ID NO: 133, and which compounds comprise at least an 8-nucleobase portion of SEQ ID No. 446, wherein the compounds specifically hybridize with the nucleic acid molecule of SEQ ID NO: 133 and inhibit the expression of HIF1α of SEQ ID NO. 133 in vitro or in vivo. The specification, claims and the art do not adequately describe the distinguishing features or attributes concisely shared by the members of this broad genus and that specifically hybridize and inhibit the expression of SEQ ID NO: 133. The specification discloses antisense oligonucleotides that are complementary to SEQ ID NO: 133. The specification does

not disclose a representative number of sequences, including any sequences with less than 100% identity to the complement of SEQ ID NO: 133, or which encompass the genus comprising compounds that are 50 nucleobases in length, which comprise 8 nucleobases of SEQ ID No. 446, and which specifically hybridize and inhibit the expression of SEQ ID No. 133 in vitro or in vivo. The genus of nucleic acids claimed encompasses a myriad of structures (*e.g.* thousands of nucleic acid sequences) and the specification and claims do not adequately teach a representative number of species for the broad genus claimed. Concise structural features that could distinguish structures within the genus from others are missing from the disclosure. No common structural attributes identify the members of the claimed genus, and distinguish members within the claimed genus from those outside of the claimed genus (*e.g.*, which among this myriad of sequences claimed successfully and specifically hybridize with the target gene of SEQ ID NO. 133 and inhibit its expression?). One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus claimed, which compounds also provide for the function claimed. Thus, Applicant was not in possession of the claimed genus.

Claims 33, 37-120 and 122-124 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the expression of HIF1α of SEQ ID NO: 133 in vitro using antisense oligonucleotides, and for inhibiting the expression of SEQ ID NO. 133 in vivo comprising the administration of antisense of SEQ ID Nos. 139, 141 and 193, does not reasonably provide enablement

for methods of inhibiting the expression of HIF1α of SEQ ID NO: 133 in vivo and which prevent or treat any disease or condition associated with the expression of SEQ ID NO: 133. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions and methods of inhibition and treatment comprising the administration of compounds that are 12-50 nucleobases in length and targeted to a nucleic acid molecule encoding HIF1α of SEQ ID NO: 133, and which compounds comprise at least an 8-nucleobase portion of SEQ ID No. 446, wherein the compounds specifically hybridize with the nucleic acid molecule of SEQ ID NO: 133 and inhibit the expression of HIF1α of SEQ ID NO. 133 in vitro or in vivo, and which prevent and treat any disease or condition associated with the expression of SEQ ID NO. 133.

The state of the prior art and the predictability or unpredictability of the art. Branch and Crooke teach that the in vivo (whole organism) application of molecules is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target molecules. (See entire text of A. Branch, Trends in Biochem. Sci., 23, 45-50, 1998; and S. Crooke, Antisense Res. & Application, Chapter 1, pages 1-50, ed. by S. Crooke, Springer-Verlag, especially pages 34-36).

Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross

biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release... remains one of the major hurdles in the field." ((See Peracchi et al, Rev. Med. Virol., 14, pages 47-64, 2004, abstract on page 47 and text on page 51).

Cellular uptake by appropriate target cells is a rate limiting step that has yet to be overcome in achieving predictable clinical efficacy. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of small molecules in vitro and in vivo (see Agrawal et al, Molecular Med. Today, Vol. 6, pages 72-81, 2000, especially at pages 79-80; see Chirila et al, Biomaterials, Vol. 23, pages 321-342, 2002, especially pages 326-327 for a general review of the important and inordinately difficult challenges of the delivery of therapeutic molecules to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. The specification teaches a method of inhibiting the expression of HIF1α of SEQ ID NO: 133 in vitro using antisense oligonucleotides, and for inhibiting the expression of SEQ ID NO. 133 in vivo comprising the administration of antisense of SEQ ID Nos. 139, 141 and 193. Applicants have not provided adequate guidance in the specification, however, toward a method of inhibiting HIF1α in vivo, and of preventing and treating any condition or disease associated with the expression of HIF1α comprising the administration of a representative number of

species of the genus comprising compounds that are 12-50 nucleobases in length and targeted to a nucleic acid molecule encoding HIF1α of SEQ ID NO: 133, and which compounds comprise at least an 8-nucleobase portion of SEQ ID No. 446. One skilled in the art would not accept on its face the examples given in the specification of the in vitro expression of HIF1α of SEQ ID NO: 133 using antisense oligonucleotides, or of the in vivo inhibition of the expression of SEQ ID NO. 133 comprising the administration of antisense of SEQ ID Nos. 139, 141 and 193 as being correlative or representative of the ability to inhibit HIF1α expression in vivo, and further whereby treatment for any disease or condition associated with expression of HIF1α compromising the administration of a representative number of species of the genus comprising compounds that are 12-50 nucleobases in length and targeted to a nucleic acid molecule encoding HIF1α of SEQ ID NO: 133, and which compounds comprise at least an 8-nucleobase portion of SEQ ID No. 446. There is a lack of guidance in the specification and an unpredictability associated with the successful targeting and delivery of nucleic acids to appropriate target cells harboring HIF1α of SEQ ID NO: 133 in an organism.

The breadth of the claims and the quantity of experimentation required. The claims are broadly drawn to compositions and methods of inhibition and treatment comprising the administration of compounds that are 12-50 nucleobases in length and targeted to a nucleic acid molecule encoding HIF1α of SEQ ID NO: 133, and which compounds comprise at least an 8-nucleobase portion of SEQ ID No. 446, wherein the compounds specifically hybridize with the nucleic acid molecule of SEQ ID NO: 133 and inhibit the expression of HIF1α of SEQ ID NO. 133 in vitro or in vivo, and which prevent

and treat any disease or condition associated with the expression of SEQ ID NO. 133. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of a representative number of compounds that are 12-50 nucleobases in length and targeted to a nucleic acid molecule encoding HIF1α of SEQ ID NO: 133, and which compounds comprise at least an 8-nucleobase portion of SEQ ID No. 446, whereby these compounds successfully inhibit the expression of HIF1α of SEQ ID NO: 133 in vitro and in vivo, and further whereby treatment effects and prevention are provided for any disease or condition associated with the expression of HIF1α of SEQ ID NO: 133. Other experimentation required to practice the invention claimed includes determining accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues in an organism, whereby the compound or compounds are effectively delivered in adequate quantities to the target cells, HIF1α of SEQ ID NO: 133 expression is inhibited and prevention or treatment effects are provided for any disease or condition associated with the expression of HIF1α of SEQ ID NO: 133. Since the specification fails to provide sufficient guidance for the methods claimed, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-7, 37 and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kung et al (EP 0147819).

Kung et al (EP 0147819) teach compositions comprising a pharmaceutically acceptable diluent and an antisense oligonucleotide compound (RNA or DNA) that is 12-50 nucleobases in length, comprises at least an 8-nucleobase portion of SEQ ID No. 446, and specifically hybridizes with SEQ ID NO. 133 (see SEQ ID No. 7 of Kung et al, see also the attached sequence alignment data between SEQ ID NO. 7 of Kung et al and SEQ ID No. 446 of the instant application). The burden of establishing whether the prior art oligonucleotide has the function of specifically binding to SEQ ID No. 133 as claimed falls to applicant. See (In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-

434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced b the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing In re Fitzgerald 205 USPQ 594, 596 (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, absent evidence to the contrary, since the oligonucleotide disclosed by Kung et al meets all of the structural limitations of the instantly claimed invention, it would necessarily be presumed to have the functionality claimed, of specifically binding to HIF1α of SEQ ID NO: 133. Therefore, absent evidence to the contrary, claims 1, 4-7, 37 and 44 are anticipated by or, in the alternative, obvious over Kung et al.

Claims 1, 4-7, 37 and 44 are rejected under 35 U.S.C. 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Baird et al (USPN 6,958,240).

Baird et al (USPN 6,958,240) teach compositions comprising a pharmaceutically acceptable diluent and an antisense oligonucleotide compound (RNA or DNA) that is

12-50 nucleobases in length, comprises at least an 8-nucleobase portion of SEQ ID No. 446, and specifically hybridizes with SEQ ID NO. 133 (see SEQ ID No. 12 of Baird et al, see also the attached sequence alignment data between SEQ ID NO. 12 of Baird et al and SEQ ID No. 446 of the instant application). The burden of establishing whether the prior art oligonucleotide has the function of specifically binding to SEQ ID NO. 133 as claimed falls to applicant. See (In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced b the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing In re Fitzgerald 205 USPQ 594, 596 (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, absent evidence to the contrary, since the oligonucleotide disclosed by Baird et al meets all of the structural limitations of the instantly claimed invention, it would necessarily be presumed to have the functionality claimed, of specifically binding to HIF1α of SEQ ID NO: 133.

Therefore, absent evidence to the contrary, claims 1, 4-7, 37 and 44 are anticipated by or, in the alternative, obvious over Baird et al.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3-8, 22-25, 33, 37 and 44 are rejected under 35 U.S.C. 102(e) as being anticipated by Usman et al (WO 2005/035759).

Usman et al (WO 2005/035759) teach the inhibition of HIF1α of SEQ ID NO: 133 in vitro comprising administration of an antisense oligonucleotide compound (RNA or DNA) that is 12-50 nucleobases in length, comprises at least an 8-nucleobase portion of SEQ ID No. 446, and specifically hybridizes with SEQ ID NO. 133 (see Acc. No. ADZ58131, SEQ ID No. 259 of Usman et al; see also the attached sequence alignment data between Acc. No. ADZ58131 of Usman et al and SEQ ID No. 446 of the instant application). Usman et al also teach modified oligonucleotides comprising 5'-methyl cytosine modified residues, phosphorothioate internucleotide linkages, 2'-O-methoxyethyl groups, and chimeric oligonucleotides, as well as compositions

comprising pharmaceutically acceptable diluents (see pp. 14, 21, 29-32, and claim 33 of Usman et al).

Allowable Subject Matter

SEQ ID NO: 446 appears free of the prior art searched and of record.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of

this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
6-22-06